

REMARKS

This Application has been carefully reviewed in light of the Office Action mailed May 10, 2005. At the time of the Office Action, Claims 1-33 were pending in this Application. Claims 2-33 were rejected. Claim 1 was allowed. Claim 34 has been added and Claims 2-5, 7, 11, 13, 16-19, and 26-27 have been amended to further define various features of Applicants' invention. No new matter is presented by these amendments. Applicants respectfully request reconsideration and favorable action in this case.

Claim Objections

Claim 5 was objected to because of informalities. Applicants amend Claim 5 to overcome this objection.

Rejections under 35 U.S.C. § 112 ¶1, Written Description

Claims 2-33 were rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Applicants agree with the Examiner's characterization of the percentage homology claims as genus claims. There may be one or more species that satisfy the % homology limitation and also the stem-regulated or defense-induced functional limitations.

However, Applicants assert that a representative number of species are adequately described for each genus. Applicants, through SEQ. ID. NO.:1, disclose at least a partial structure for each species. Further, Applicants provide a functional characteristic (stem-regulation) that applies to each species and is correlated with structure.

A similar issue was recently addressed in *Capon v. Dudas*, Slip Opinion 03-1480, -1481 (Fed. Cir., August 12, 2005), a copy of which is attached for the Examiner's convenience. In *Capon*, the Board rejected claims to chimeric genes based on an alleged lack of written description. The Board's decision was soundly reversed by the Federal Circuit, which was persuaded in part by the fact that the "specifications provide for evaluation of the effectiveness of their chimeric combinations." *Id.* at 16. Applicants provide, by way of the Examples and elsewhere in the specification, ample description for evaluation of the effectiveness of particular promoter having at least 60% homology to SEQ. ID. NO.: 1 and,

by provision of SEQ. ID. NO.: 1, also provide at least a portion of the sequence of these variant promoters.

Accordingly, Applicants submit that Claims 2-33 and all other claims, as amended or added, that recite particular degrees of sequence homology are described in the specification in sufficient detail to meet the written description requirement. Allowance of all claims is respectfully requested.

Rejections under 35 U.S.C. § 112 ¶1, Enablement

Claims 2-33 were rejected by the Examiner under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicants believe one of skill in the art would readily be able to make and use all claimed embodiments of the invention with the guidance of the present specification.

First Applicants note that the level of skill is generally included in the predictability of the art when addressing the Wands factors. The level of skill here is quite high, with most practitioners being at least Ph.D. candidate graduate students if not scientists already holding a Ph.D. Accordingly, the level of direction required by one skilled in the art is low.

Further, the specification, through the cited examples, provides very detailed descriptions of how to test promoters to determine whether they function as a stem-regulated or defense-induced promoter or not. MPEP §2164.06 states that the test for undue experimentation “is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.” As an example of reasonable experimentation, the MPEP goes on to cite an invention in which “one embodiment... and the method to determine dose/response was set forth in the specification, the specification was enabling.

Here, the Examples provide a ready way to test the claimed sequences to determine if the functional limitation is met. Thus, while a substantial quantity of experimentation may well be needed to identify all promoters meeting the claim limitations, this experimentation merely involves plugging new sequences into methods that are well-

known or described in the specification. The specification provides very detailed descriptions of ways to determine if the desired results have been obtained.

Trial and error experimentation may be required to determine all of the sequences that meet the claim limitations, but the quantity of that experimentation is not so much as to be undue because it does not require anything other than trial and error and is thus routine. Further, Applicants note that with modern advances in microbiological techniques available at the time the present application was filed, the creation of various promoters having different sequences and of constructions useful to test these sequences may well have been amenable to some degree of automation.

Finally, the Examiner has asserted that the invention is enabled only for sugarcane and rice because examples are provided only for those plants. Applicants submit, however, that based on the data provided for sugarcane and rice one skilled in the art would also expect the promoter to be operable at least in other monocots. Accordingly, Applicants have amended the claims to recite monocot plants.

Applicants accordingly assert that, given the high level of skill in the art and the detailed description of ways to test promoter sequences to determine if claim limitation are met, undue experimentation is not required to make and use the claimed invention. Allowance of all claims is requested.

Rejections under 35 U.S.C. §112, ¶2, Indefiniteness

Claims 3-33 were rejected as indefinite for failing to particularly point out and describe the invention. Specifically, the Examiner has indicated that the use of the term "OMT" should be defined within the claims. Applicants believe that in light of the amendments to recite sequence homology the term "OMT" is no longer needed in the claims and have cancelled it from all claims.

The Examiner has also indicated that Claims 19 and 27 are indefinite because of the term "expression nucleic acid in an expression vector". These claims have been amended to clarify that the OMT promoter is part of the expression vector.

Specification

The Examiner objected to the specification for a misspelling of the word “identify”, which has been corrected.

The Examiner objected to Claim 10 as too dark, new color and black and while copies have been provided.

The Examiner objected to the legends in Figures 5, 7-9, 11, 13 and 14. Applicants have removed legends from all but Figures 5 and 8. In Figure 5, the legend must be included in the figure because it must contain color components. There is no way to convey the color components in the text of the specification. In Figure 8, the row labels must be included for the figure to be understandable.

Figure 9 has been relabeled to have Figure 9A and Figure 9B components.

Allowable Subject Matter

Claim 1 is allowable.

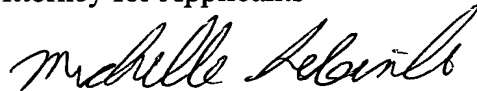
CONCLUSION

Applicants have now made an earnest effort to place this case in condition for allowance in light of the amendments and remarks set forth above. Applicants respectfully request reconsideration of the claims as amended.

Applicants enclose a Petition for One Month Extension of Time, and a check in the amount of \$60.00 for the extension fee. Applicants believe there are no additional fees due at this time, however, the Commissioner is hereby authorized to charge any fees necessary or credit any overpayment to Deposit Account No. 02-0384 of Baker Botts L.L.P.

If there are any matters concerning this Application that may be cleared up in a telephone conversation, please contact Applicants' attorney at 512.322.2580.

Respectfully submitted,
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Date: 9/9/05

ATTORNEY DOCKET
017575.0774 (TAMUS 1910)

PATENT APPLICATION
10/751,612

19

APPENDIX

ATTORNEY DOCKET
017575.0774 (TAMUS 1910)

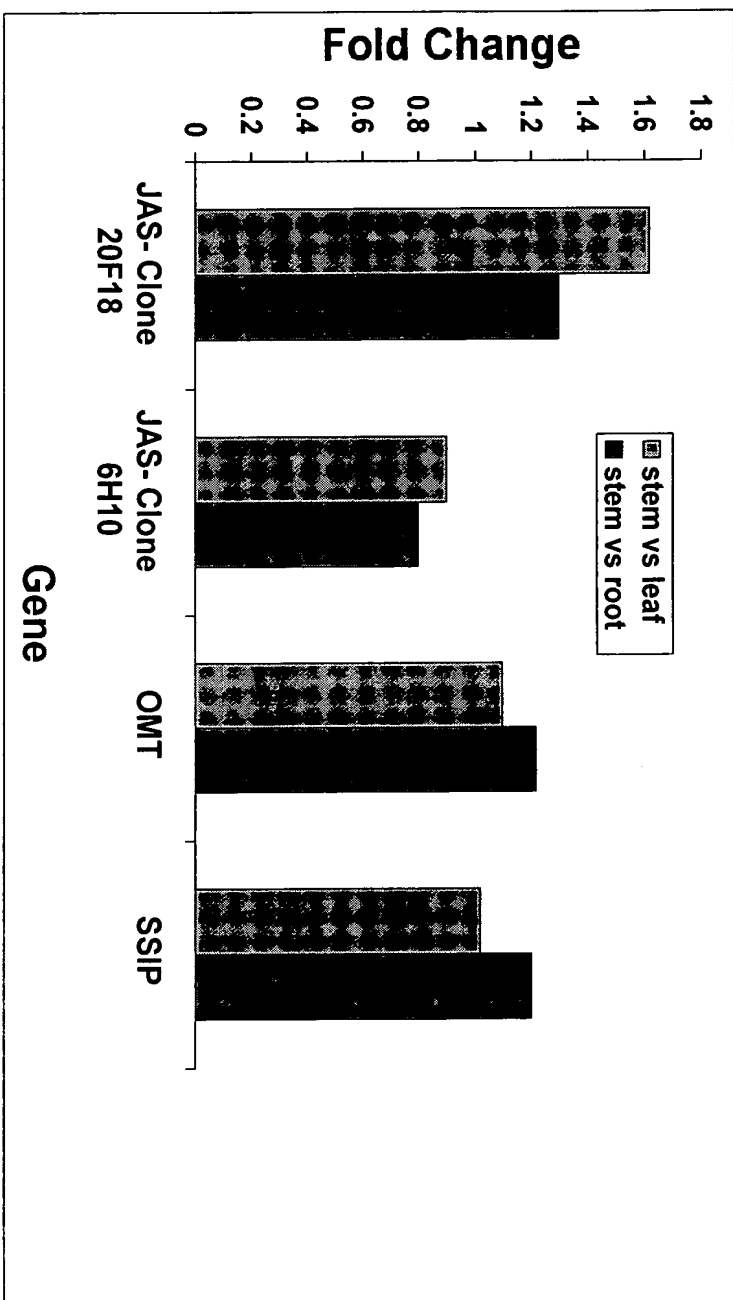
PATENT APPLICATION
10/751,612

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DRAWING AMENDMENT

Please replace Figures 7, 9-11, 13 and 14 with the enclosed amended drawings.
Applicant respectfully submits that no new matter has been added.

FIGURE 7



Real-time RT-PCR quantitations (Ct values)
are normalized to
the endogenous control ubiquitin (constitutive gene)

Legend Removed

FIGURE 9A
EcoRI NotI

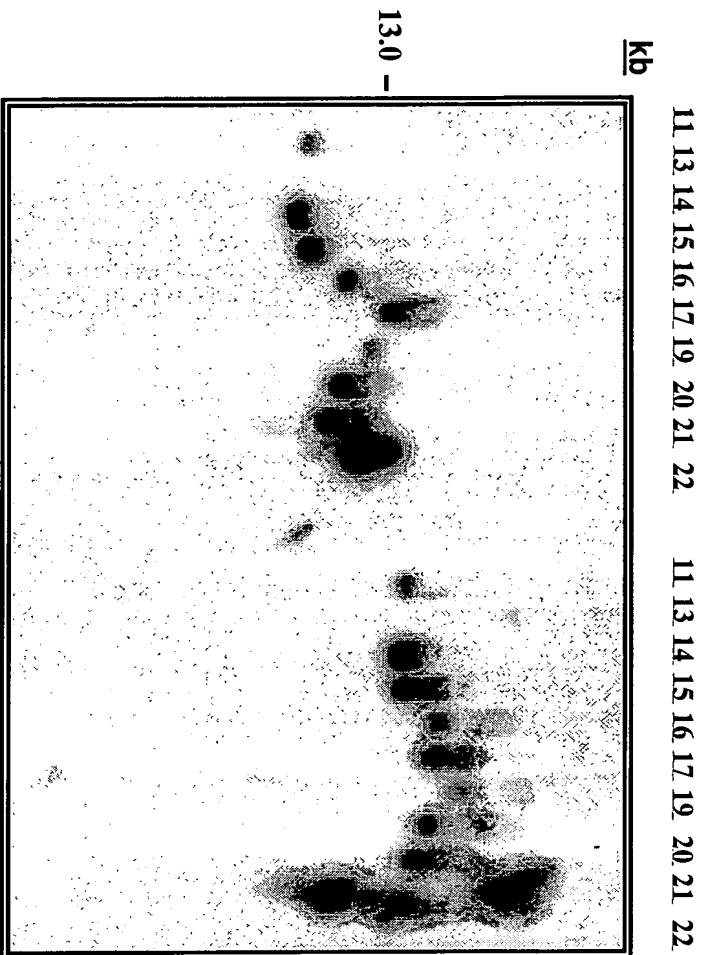
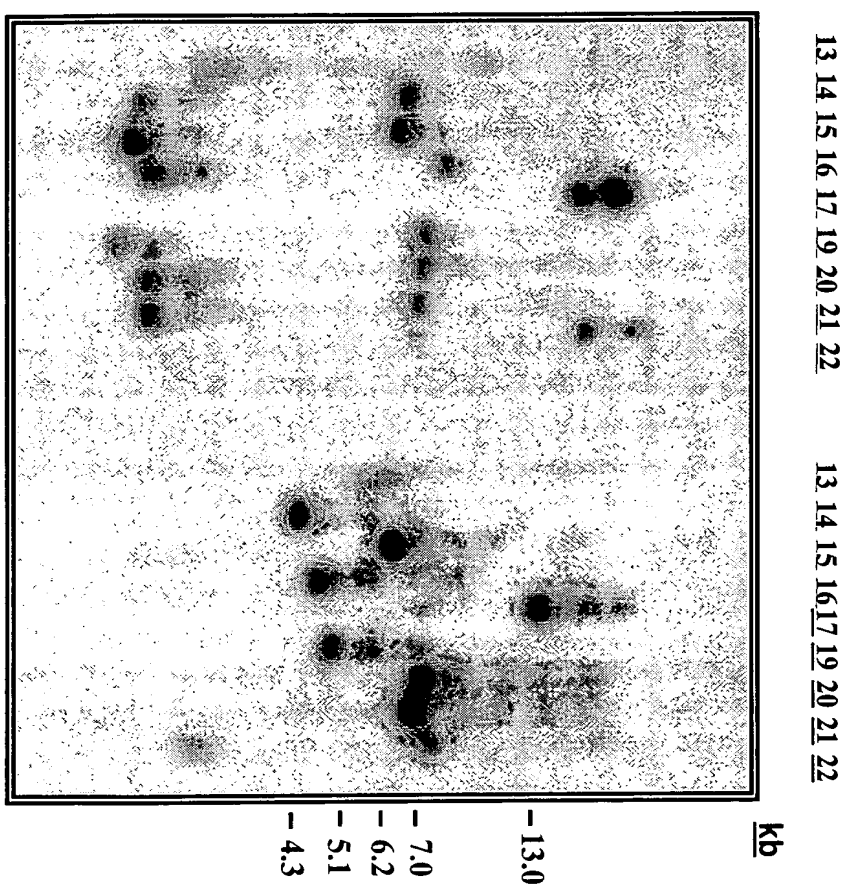


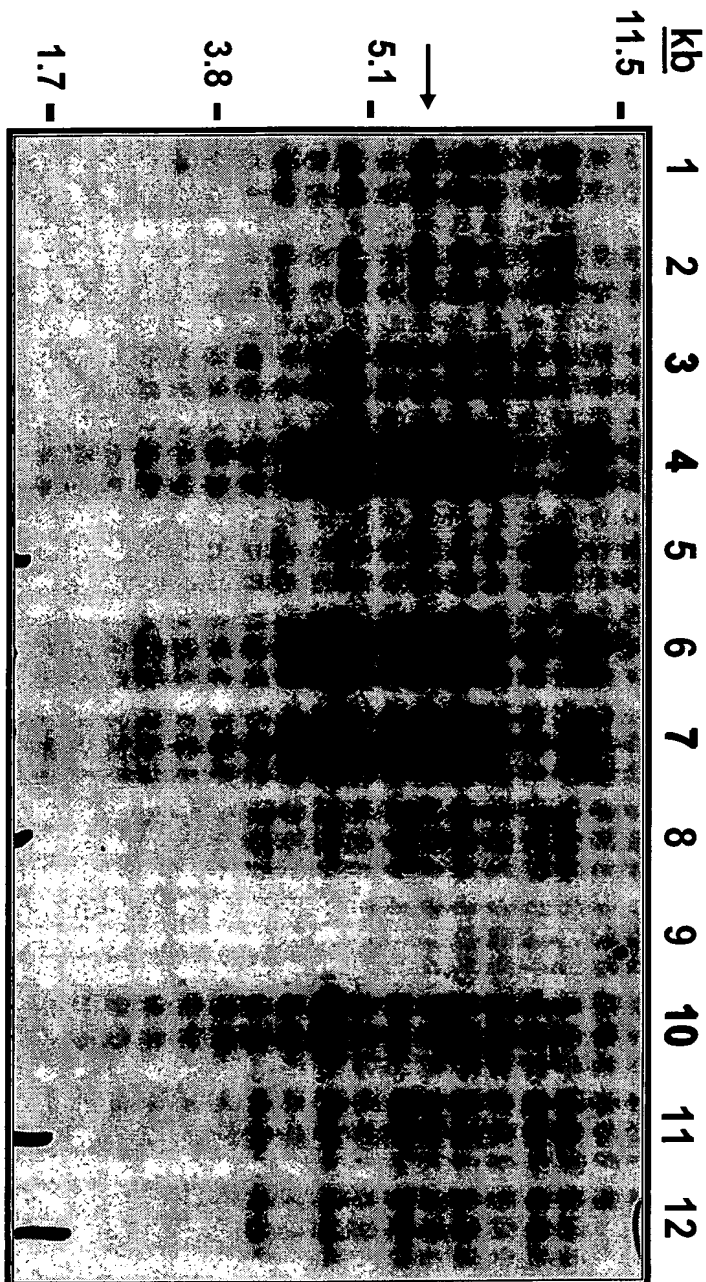
FIGURE 9B ¹³¹I Added
HindIII XbaI



OMT full-length cDNA probe

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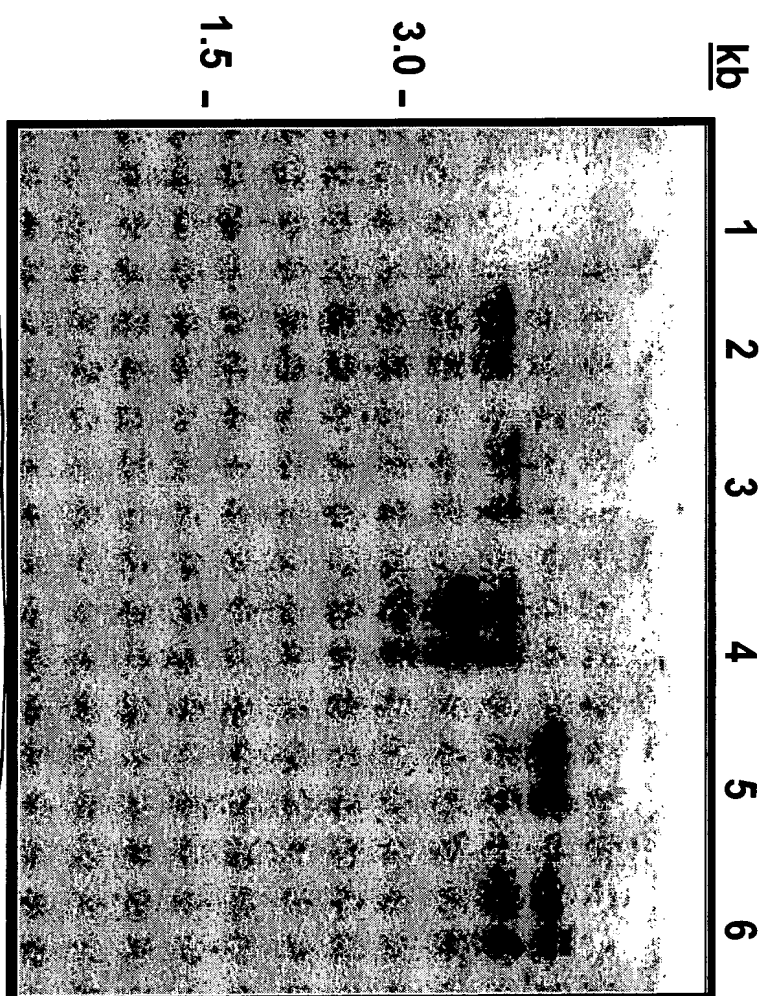
FIGURE 11



HindIII digested sugarcane genomic DNA hybridized with GUS gene probe.
Lanes 1, 2, 5, 8, 11 & 12: One positive transformation event;
Lanes 4, 6 & 7: Another positive event; Lanes 3 & 10: A negative event.

Legend Remove

FIGURE 13



Phosphorimage of DNA gel Blot

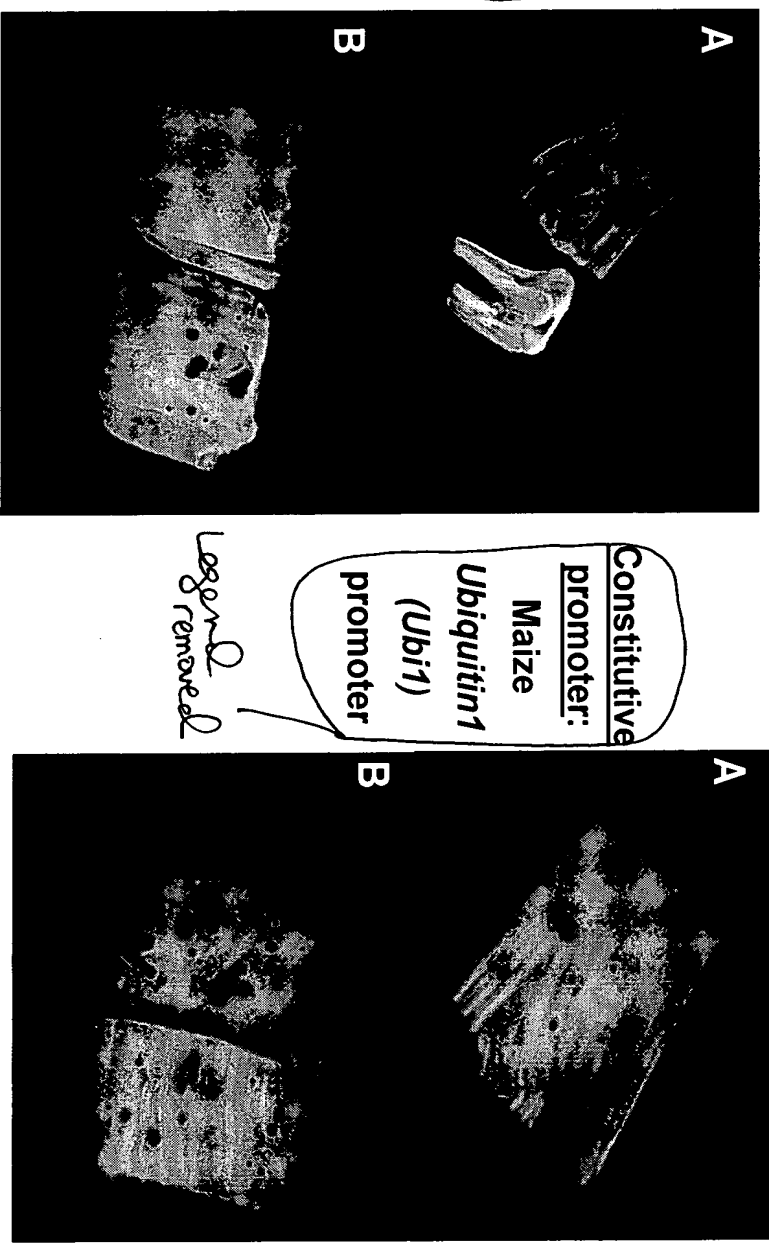
HindIII digested rice genomic DNA hybridized to hygromycin gene probe.

Lane 1: Untransformed plant; Lanes 2, 3, 4 & 5: 3 independent

POMT1::GUS lines; Lane 6: one POMT2::GUS line.

Legend removed

FIGURE 14
sorghum (RPx430) and maize (B73) stem cells



Stem regulated
promoter:
Sugarcane OMT
promoter

sorghum (A) and maize (B)

Constitutive
promoter:
Maize
Ubiquitin1
(Ubi1)
promoter

sorghum (A) and maize (B)

United States Court of Appeals for the Federal Circuit



03-1480, -1481
(Interference No. 103,887)

DANIEL J. CAPON, ARTHUR WEISS, BRIAN A. IRVING,
MARGO R. ROBERTS, and KRISZTINA ZSEBO,

Appellants,

v.

ZELIG ESHHAR, DANIEL SCHINDLER, TOVA WAKS,
and GIDEON GROSS,

Cross-Appellants,

v.

JON DUDAS, Director of the Patent and Trademark Office,

Intervenor.

Steven B. Kelber, Piper Rudnick, LLP, of Washington, DC, argued for appellants.

Roger L. Browdy, Browdy and Neimark, P.L.L.C., of Washington, DC, argued for cross-appellants.

Mary L. Kelly, Associate Solicitor, Office of the Solicitor, United States Patent and Trademark Office, of Arlington, Virginia, argued for intervenor. With her on the brief were John M. Whealan, Solicitor and Stephen Walsh, Associate Solicitor.

Appealed from: United States Patent and Trademark Office Board of Patent Appeals
and Interferences

United States Court of Appeals for the Federal Circuit

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DANIEL J. CAPON, ARTHUR WEISS, BRIAN A. IRVING,
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ZELIG ESHHAR, DANIEL SCHINDLER, TOVA WAKS,
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v.

JON DUDAS,
Director of the Patent and Trademark Office,
Intervenor.

DECIDED: August 12, 2005

Before NEWMAN, MAYER,* and GAJARSA, Circuit Judges.

NEWMAN, Circuit Judge.

Both of the parties to a patent interference proceeding have appealed the decision of the Board of Patent Appeals and Interferences of the United States Patent and Trademark Office, wherein the Board held that the specification of neither party met the written description requirement of the patent statute. Capon v. Eshhar, Interf. No. 103,887

* Haldane Robert Mayer vacated the position of Chief Judge on December 24, 2004.

(Bd. Pat. App. & Interf. Mar. 26, 2003). The Board dissolved the interference and cancelled all of the claims of both parties corresponding to the interference count. With this ruling, the Board terminated the proceeding and did not reach the question of priority of invention. We conclude that the Board erred in its application of the law of written description. The decision is vacated and the case is remanded to the Board for further proceedings.

BACKGROUND

Daniel J. Capon, Arthur Weiss, Brian A. Irving, Margo R. Roberts, and Krisztina Zsebo (collectively "Capon") and Zelig Eshhar, Daniel Schindler, Tova Waks, and Gideon Gross (collectively "Eshhar") were the parties to an interference proceeding between Capon's United States Patent No. 6,407,221 ("the '221 patent") entitled "Chimeric Chains for Receptor-Associated Signal Transduction Pathways" and Eshhar's patent application Serial No. 08/084,994 ("the '994 application") entitled "Chimeric Receptor Genes and Cells Transformed Therewith." Capon's Patent No. 5,359,046 ("the '046 patent"), parent of the '221 patent, was also included in the interference but was held expired for non-payment of a maintenance fee. The PTO included the '046 patent in its decision and in its argument of this appeal.¹

A patent interference is an administrative proceeding pursuant to 35 U.S.C. §§102(g) and 135(a), conducted for the purpose of determining which of competing applicants is the first inventor of common subject matter. An interference is instituted after the separate

¹ Although Capon is designated as appellant and Eshhar as cross-appellant, both appealed the Board's decision. See Fed. R. App. P. 28(h). The Director of the PTO intervened to support the Board, and has fully participated in this appeal.

patent applications have been examined and found to contain patentable subject matter. Capon's patents had been examined and had issued before this interference was instituted, and Eshhar's application had been examined and allowed but a patent had not yet issued.

During an interference proceeding the Board is authorized to determine not only priority of invention but also to redetermine patentability. 35 U.S.C. §6(b). The question of patentability of the claims of both parties was raised *sua sponte* by an administrative patent judge during the preliminary proceedings. Thereafter the Board conducted an *inter partes* proceeding limited to this question, receiving evidence and argument. The Board then invalidated all of the claims that had been designated as corresponding to the count of the interference, viz., all of the claims of the Capon '221 patent, claims 5-8 of the Capon '046 patent, and claims 1-7, 9-20, and 23 of the Eshhar '994 application.

In accordance with the Administrative Procedure Act, the law as interpreted and applied by the agency receives plenary review on appeal, and the agency's factual findings are reviewed to determine whether they were arbitrary, capricious, or unsupported by substantial evidence in the administrative record. See 5 U.S.C. §706(2); Dickinson v. Zurko, 527 U.S. 150, 164-65 (1999); In re Gartside, 203 F.3d 1305, 1315 (Fed. Cir. 2000).

The Invention

A chimeric gene is an artificial gene that combines segments of DNA in a way that does not occur in nature. The '221 patent and '994 application are directed to the production of chimeric genes designed to enhance the immune response by providing cells with specific cell-surface antibodies in a form that can penetrate diseased sites, such as solid tumors, that were not previously reachable. The parties explain that their invention is

a way of endowing immune cells with antibody-type specificity, by combining known antigen-binding-domain producing DNA and known lymphocyte-receptor-protein producing DNA into a unitary gene that can express a unitary polypeptide chain. Eshhar summarized the problem to which the invention is directed:

Antigen-specific effector lymphocytes, such as tumor-specific T cells, are very rare, individual-specific, limited in their recognition spectrum and difficult to obtain against most malignancies. Antibodies, on the other hand, are readily obtainable, more easily derived, have wider spectrum and are not individual-specific. The major problem of applying specific antibodies for cancer immunotherapy lies in the inability of sufficient amounts of monoclonal antibodies (mAb) to reach large areas within solid tumors.

Technical Paper Explaining Eshhar's Invention, at 6.

The inventions of Capon and Eshhar are the chimeric DNA that encodes single-chain chimeric proteins for expression on the surface of cells of the immune system, plus expression vectors and cells transformed by the chimeric DNA. The experts for both parties explain that the invention combines selected DNA segments that are both endogenous and nonendogenous to a cell of the immune system, whereby the nonendogenous segment encodes the single-chain variable ("scFv") domain of an antibody, and the endogenous segment encodes cytoplasmic, transmembrane, and extracellular domains of a lymphocyte signaling protein. They explain that the scFv domain combines the heavy and light variable ("Fv") domains of a natural antibody, and thus has the same specificity as a natural antibody. Linking this single chain domain to a lymphocyte signaling protein creates a chimeric scFv-receptor ("scFvR") gene which, upon transfection into a cell of the immune system, combines the specificity of an antibody with the tissue penetration, cytokine production, and target-cell destruction capability of a lymphocyte.

The parties point to the therapeutic potential if tumors can be infiltrated with specifically designed immune cells of appropriate anti-tumor specificity.

The Eshhar Claims

The Board held unpatentable the following claims of Eshhar's '994 application; these were all of the '994 claims that had been designated as corresponding to the count of the interference. Eshhar's claim 1 was the designated count.

1. A chimeric gene comprising
 - a first gene segment encoding a single-chain Fv domain (scFv) of a specific antibody and
 - a second gene segment encoding partially or entirely the transmembrane and cytoplasmic, and optionally the extracellular, domains of an endogenous protein
 - wherein said endogenous protein is expressed on the surface of cells of the immune system and triggers activation and/or proliferation of said cells, which chimeric gene, upon transfection to said cells of the immune system, expresses said scFv domain and said domains of said endogenous protein in one single chain on the surface of the transfected cells such that the transfected cells are triggered to activate and/or proliferate and have MHC nonrestricted antibody-type specificity when said expressed scFv domain binds to its antigen.
2. A chimeric gene according to claim 1 wherein the second gene segment further comprises partially or entirely the extracellular domain of said endogenous protein.
3. A chimeric gene according to claim 1 wherein the first gene segment encodes the scFv domain of an antibody against tumor cells.
4. A chimeric gene according to claim 1 wherein the first gene segment encodes the scFv domain of an antibody against virus infected cells.
5. A chimeric gene according to claim 4 wherein the virus is HIV.
6. A chimeric gene according to claim 1 wherein the second gene segment encodes a lymphocyte receptor chain.
7. A chimeric gene according to claim 6 wherein the second gene segment encodes a chain of the T cell receptor.

9. A chimeric gene according to claim 7 wherein the second gene segment encodes the α , β , γ , or δ chain of the antigen-specific T cell receptor.
10. A chimeric gene according to claim 1 wherein the second gene segment encodes a polypeptide of the TCR/CD3 complex.
11. A chimeric gene according to claim 10 wherein the second gene segment encodes the zeta or eta isoform chain.
12. A chimeric gene according to claim 1 wherein the second gene segment encodes a subunit of the Fc receptor or IL-2 receptor.
13. A chimeric gene according to claim 12 wherein the second gene segment encodes a common subunit of IgE and IgG binding Fc receptors.
14. A chimeric gene according to claim 13 wherein said subunit is the gamma subunit.
15. A chimeric gene according to claim 13 wherein the second gene segment encodes the CD16 α chain of the Fc γ RIII or Fc γ RII.
16. A chimeric gene according to claim 12 wherein the second gene segment encodes the α or β subunit of the IL-2 receptor.
17. An expression vector comprising a chimeric gene according to claim 1.
18. A cell of the immune system endowed with antibody specificity transformed with an expression vector according to claim 17.
19. A cell of the immune system endowed with antibody specificity comprising a chimeric gene according to claim 1.
20. A cell of the immune system according to claim 19 selected from the group consisting of a natural killer cell, a lymphokine activated killer cell, a cytotoxic T cell, a helper T cell and a subtype thereof.
23. A chimeric gene according to claim 1 wherein said endogenous protein is a lymphocyte receptor chain, a polypeptide of the TCR/CD3 complex, or a subunit of the Fc or IL-2 receptor.

The Board did not discuss the claims separately, and held that the specification failed to satisfy the written description requirement as to all of these claims.

The Capon Claims

Claims 1-10, all of the claims of the '221 patent, were held unpatentable on written description grounds. Claims 1-6 are directed to the chimeric DNA, claims 7, 8, and 10 to the corresponding cell comprising the DNA, and claim 9 to the chimeric protein:

1. A chimeric DNA encoding a membrane bound protein, said chimeric DNA comprising in reading frame:

DNA encoding a signal sequence which directs said membrane bound protein to the surface membrane;

DNA encoding a non-MHC restricted extracellular binding domain which is obtained from a single chain antibody that binds specifically to at least one ligand, wherein said at least one ligand is a protein on the surface of a cell or a viral protein;

DNA encoding a transmembrane domain which is obtained from a protein selected from the group consisting of CD4, CD8, immunoglobulin, the CD3 zeta chain, the CD3 gamma chain, the CD3 delta chain and the CD3 epsilon chain; and

DNA encoding a cytoplasmic signal-transducing domain of a protein that activates an intracellular messenger system which is obtained from CD3 zeta,

wherein said extracellular domain and said cytoplasmic domain are not naturally joined together, and said cytoplasmic domain is not naturally joined to an extracellular ligand-binding domain, and when said chimeric DNA is expressed as a membrane bound protein in a host cell under conditions suitable for expression, said membrane bound protein initiates signaling in said host cell when said extracellular domain binds said at least one ligand.

2. The DNA of claim 1, wherein said single-chain antibody recognizes an antigen selected from the group consisting of viral antigens and tumor cell associated antigens.

3. The DNA of claim 2 wherein said single-chain antibody is specific for the HIV env glycoprotein.

4. The DNA of claim 1, wherein said transmembrane domain is naturally joined to said cytoplasmic domain.

5. An expression cassette comprising a transcriptional initiation region, the DNA of claim 1 under the transcriptional control of said transcriptional initiation region, and a transcriptional termination region.

6. A retroviral RNA or DNA construct comprising the expression cassette of claim 5.
7. A cell comprising the DNA of claim 1.
8. The cell of claim 7, wherein said cell is a human cell.
9. A chimeric protein comprising in the N-terminal to C-terminal direction:
 - a non-MHC restricted extracellular binding domain which is obtained from a single chain antibody that binds specifically to at least one ligand, wherein said at least one ligand is a protein on the surface of a cell or a viral protein;
 - a transmembrane domain which is obtained from a protein selected from the group consisting CD4, CD8, immunoglobulin, the CD3 zeta chain, the CD3 gamma chain, the CD3 delta chain and the CD3 epsilon chain; and
 - a cytoplasmic signal-transducing domain of a protein that activates an intracellular messenger system which is obtained from CD3 zeta,wherein said extracellular domain and said cytoplasmic domain are not naturally joined together, and said cytoplasmic domain is not naturally joined to an extracellular ligand-binding domain, and when said chimeric protein is expressed as a membrane bound protein in a host cell under conditions suitable for expression, said membrane bound protein initiates signaling in said host cell when said extracellular domain binds said at least one ligand.
10. A mammalian cell comprising as a surface membrane protein, the protein of claim 9.

In addition, claims 5, 6, 7, and 8 of Capon's '046 patent were held unpatentable. These claims are directed to chimeric DNA sequences where the encoded extracellular domain is a single-chain antibody containing ligand binding activity.

The Board Decision

The Board presumed enablement by the specifications of the '221 patent and '994 application of the full scope of their claims, and based its decision solely on the ground of

failure of written description. The Board held that neither party's specification provides the requisite description of the full scope of the chimeric DNA or encoded proteins, by reference to knowledge in the art of the "structure, formula, chemical name, or physical properties" of the DNA or the proteins. In the Board's words:

We are led by controlling precedent to understand that the full scope of novel chimeric DNA the parties claim is not described in their specifications under 35 U.S.C. §112, first paragraph, by reference to contemporary and/or prior knowledge in the art of the structure, formula, chemical name, or physical properties of many protein domains, and/or DNA sequences which encode many protein domains, which comprise single-chain proteins and/or DNA constructs made in accordance with the plans, schemes, and examples thereof the parties disclose.

Bd. op. at 4. As controlling precedent the Board cited Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997); Fiers v. Revel Co., 984 F.2d 1164 (Fed. Cir. 1993); Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (Fed. Cir. 1991); and Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316 (Fed. Cir. 2002). The Board summarized its holding as follows:

Here, both Eshhar and Capon claim novel genetic material described in terms of the functional characteristics of the protein it encodes. Their specifications do not satisfy the written description requirement because persons having ordinary skill in the art would not have been able to visualize and recognize the identity of the claimed genetic material without considering additional knowledge in the art, performing additional experimentation, and testing to confirm results.

Bd. op. at 89.

DISCUSSION

Eshhar and Capon challenge both the Board's interpretation of precedent and the Board's ruling that their descriptions are inadequate. Both parties explain that their

chimeric genes are produced by selecting and combining known heavy- and light-chain immune-related DNA segments, using known DNA-linking procedures. The specifications of both parties describe procedures for identifying and obtaining the desired immune-related DNA segments and linking them into the desired chimeric genes. Both parties point to their specific examples of chimeric DNA prepared using identified known procedures, along with citation to the scientific literature as to every step of the preparative method.

The parties presented expert witnesses who placed the invention in the context of prior knowledge and explained how the descriptive text would be understood by persons of skill in the field of the invention. The witnesses explained that the principle of forming chimeric genes from selected segments of DNA was known, as well as their methods of identifying, selecting, and combining the desired segments of DNA. Dr. Eshhar presented an expert statement wherein he explained that the prior art contains extensive knowledge of the nucleotide structure of the various immune-related segments of DNA; he stated that over 785 mouse antibody DNA light chains and 1,327 mouse antibody DNA heavy chains were known and published as early as 1991. Similarly Capon's expert Dr. Desiderio discussed the prior art, also citing scientific literature:

The linker sequences disclosed in the '221 patent (col. 24, lines 4 and 43) used to artificially join a heavy and light chain nucleic acid sequence and permit functional association of the two ligand binding regions were published by 1990, as were the methods for obtaining the mature sequences of the desired heavy and light chains for constructing a SAb (Exhibit 47, Batra et al., J., Biol. Chem., 1990; Exhibit 48, Bird et al., Science, 1988; Exhibit 50, Huston et al., PNAS, 1988; Exhibit 51, Chaudhary, PNAS, 1990, Exhibit 56, Morrison et al., Science, 1985; Exhibit 53, Sharon et al., Nature 1984).

Desiderio declaration at 4 ¶11.

Both parties stated that persons experienced in this field would readily know the structure of a chimeric gene made of a first segment of DNA encoding the single-chain variable region of an antibody, and a second segment of DNA encoding an endogenous protein. They testified that re-analysis to confirm these structures would not be needed in order to know the DNA structure of the chimeric gene, and that the Board's requirement that the specification must reproduce the "structure, formula, chemical name, or physical properties" of these DNA combinations had been overtaken by the state of the science. They stated that where the structure and properties of the DNA components were known, reanalysis was not required.

Eshhar's specification contains the nucleotide sequences of sixteen different receptor primers and four different scFv primers from which chimeric genes encoding scFvR may be obtained, while Capon's specification cites literature sources of such information. Eshhar's specification shows the production of chimeric genes encoding scFvR using primers, as listed in Eshhar's Table I. Capon stated that natural genes are isolated and joined using conventional methods, such as the polymerase chain reaction or cloning by primer repair. Capon, like Eshhar, discussed various known procedures for identifying, obtaining, and linking DNA segments, accompanied by experimental examples. The Board did not dispute that persons in this field of science could determine the structure or formula of the linked DNA from the known structure or formula of the components.

The Board stated that "controlling precedent" required inclusion in the specification of the complete nucleotide sequence of "at least one" chimeric gene. Bd. op. at 4. The Board also objected that the claims were broader than the specific examples. Eshhar and

Capon each responds by pointing to the scientific completeness and depth of their descriptive texts, as well as to their illustrative examples. The Board did not relate any of the claims, broad or narrow, to the examples, but invalidated all of the claims without analysis of their scope and the relation of claim scope to the details of the specifications.

Eshhar and Capon both argue that they have set forth an invention whose scope is fully and fairly described, for the nucleotide sequences of the DNA in chimeric combination is readily understood to contain the nucleotide sequences of the DNA components. Eshhar points to the general and specific description in his specification of known immune-related DNA segments, including the examples of their linking. Capon points similarly to his description of selecting DNA segments that are known to express immune-related proteins, and stresses the existing knowledge of these segments and their nucleotide sequences, as well as the known procedures for selecting and combining DNA segments, as cited in the specification.

Both parties argue that the Board misconstrued precedent, and that precedent does not establish a *per se* rule requiring nucleotide-by-nucleotide re-analysis when the structure of the component DNA segments is already known, or readily determined by known procedures.

The Statutory Requirement

The required content of the patent specification is set forth in Section 112 of Title 35:

§112 ¶1. The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full,

clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. See Enzo Biochem, 296 F.3d at 1330 (the written description requirement "is the quid pro quo of the patent system; the public must receive meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time"); Reiffin v. Microsoft Corp., 214 F.3d 1342, 1345-46 (Fed. Cir. 2000) (the purpose of the written description requirement "is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification"); In re Barker, 559 F.2d 588, 592 n.4 (CCPA 1977) (the goal of the written description requirement is "to clearly convey the information that an applicant has invented the subject matter which is claimed"). The written description requirement thus satisfies the policy premises of the law, whereby the inventor's technical/scientific advance is added to the body of knowledge, as consideration for the grant of patent exclusivity.

The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence. The law must be applied to each invention that enters the patent process, for each patented advance is novel in relation to the state of the science. Since the law is applied to each invention in view of the state of relevant knowledge, its application will vary

with differences in the state of knowledge in the field and differences in the predictability of the science.

For the chimeric genes of the Capon and Eshhar inventions, the law must take cognizance of the scientific facts. The Board erred in refusing to consider the state of the scientific knowledge, as explained by both parties, and in declining to consider the separate scope of each of the claims. None of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., Regents v. Lilly, Fiers v. Revel, Amgen, or Enzo Biochem, require a re-description of what was already known. In Lilly, 119 F.3d at 1567, the cDNA for human insulin had never been characterized. Similarly in Fiers, 984 F.2d at 1171, much of the DNA sought to be claimed was of unknown structure, whereby this court viewed the breadth of the claims as embracing a "wish" or research "plan." In Amgen, 927 F.2d at 1206, the court explained that a novel gene was not adequately characterized by its biological function alone because such a description would represent a mere "wish to know the identity" of the novel material. In Enzo Biochem, 296 F.3d at 1326, this court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1332 (Fed. Cir. 2003) the court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." These evolving principles were applied in Noelle v. Lederman, 355 F.3d 1343, 1349 (Fed. Cir. 2004), where the court affirmed that the human antibody there at issue was not adequately described by the structure and function of the mouse antigen; and in University of Rochester v. G.D. Searle & Co., 358 F.3d 916, 925-26 (Fed.

Cir. 2004), where the court affirmed that the description of the COX-2 enzyme did not serve to describe unknown compounds capable of selectively inhibiting the enzyme.

The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. When the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined afresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result.

The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution. Both Eshhar and Capon explain that this invention does not concern the discovery of gene function or structure, as in Lilly. The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance. The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes.

Claim Scope

There remains the question of whether the specifications adequately support the breadth of all of the claims that are presented. The Director argues that it cannot be known whether all of the permutations and combinations covered by the claims will be effective for the intended purpose, and that the claims are too broad because they may include inoperative species. The inventors say that they have provided an adequate description and exemplification of their invention as would be understood by persons in the field of the invention. They state that biological properties typically vary, and that their specifications provide for evaluation of the effectiveness of their chimeric combinations.

It is well recognized that in the "unpredictable" fields of science, it is appropriate to recognize the variability in the science in determining the scope of the coverage to which the inventor is entitled. Such a decision usually focuses on the exemplification in the specification. See, e.g., Enzo Biochem, 296 F.3d at 1327-28 (remanding for district court to determine "[w]hether the disclosure provided by the three deposits in this case, coupled with the skill of the art, describes the genera of claims 1-3 and 5"); Lilly, 119 F.3d at 1569 (genus not described where "a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus" had not been provided); In re Gostelli, 872 F.2d 1008, 1012 (Fed. Cir. 1989) (two chemical compounds were insufficient description of subgenus); In re Smith, 458 F.2d 1389, 1394-95 (CCPA 1972) (disclosure of genus and one species was not sufficient description of intermediate subgenus); In re Grimme, 274 F.2d 949, 952 (CCPA 1960) (disclosure of single example and statement of scope sufficient disclosure of subgenus).

Precedent illustrates that the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing

knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter. See, e.g., In re Wallach, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004) (an amino acid sequence supports "the entire genus of DNA sequences" that can encode the amino acid sequence because "the state of the art has developed" such that it is a routine matter to convert one to the other); University of Rochester, 358 F.3d at 925 (considering whether the patent disclosed the compounds necessary to practice the claimed method, given the state of technology); Singh v. Brake, 317 F.3d 1334, 1343 (Fed. Cir. 2002) (affirming adequacy of disclosure by distinguishing precedent in which the selection of a particular species within the claimed genus had involved "highly unpredictable results").

It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. See In re Angstadt, 537 F.2d 498, 504 (CCPA 1976) ("The examples, both operative and inoperative, are the best guidance this art permits, as far as we can conclude from the record"). While the Board is correct that a generic invention requires adequate support, the sufficiency of the support must be determined in the particular case. Both Eshhar and Capon present not only general teachings of how to select and recombine the DNA, but also specific examples of the production of specified chimeric genes. For example, Eshhar points out that in Example 1 of his specification the FcRγ chain was used, which chain was amplified from a human cDNA clone, using the procedure of Kuster, H. et al., J. Biol. Chem., 265:6448-6451 (1990), which is cited in the specification and reports the complete sequence of the FcRγ

chain. Eshhar's Example 1 also explains the source of the genes that provide the heavy and light chains of the single chain antibody, citing the PhD thesis of Gideon Gross, a co-inventor, which cites a reference providing the complete sequence of the Sp6 light chain gene used to construct the single-chain antibody. Eshhar states that the structure of the Sp6 heavy chain antibody was well known to those of skill in the art and readily accessible on the internet in a database as entry EMBL:MMSP6718. Example 5 at page 54 of the Eshhar specification cites Ravetch et al., J. Exp. Med., 170:481-497 (1989) for the method of producing the CD16 α DNA clone that was PCR amplified; this reference published the complete DNA sequence of the CD16 α chain, as discussed in paragraph 43 of the Eshhar Declaration. Example 3 of the Eshhar specification uses the DNA of the monoclonal anti-HER2 antibody and states that the N29 hybridoma that produces this antibody was deposited with the Collection Nationale de Cultures de Microorganismes, Institut Pasteur, Paris, on August 19, 1992, under Deposit No. CNCM I-1262. It is incorrect to criticize the methods, examples, and referenced prior art of the Eshhar specification as but "a few PCR primers and probes," as does the Director's brief.

Capon's Example 3 provides a detailed description of the creation and expression of single chain antibody fused with T-cell receptor zeta chain, referring to published vectors and procedures. Capon, like Eshhar, describes gene segments and their ligation to form chimeric genes. Although Capon includes fewer specific examples in his specification than does Eshhar, both parties used standard systems of description and identification, as well as known procedures for selecting, isolating, and linking known DNA segments. Indeed, the Board's repeated observation that the full scope of all of the claims appears to be "enabled" cannot be reconciled with the Board's objection that only a "general plan" to

combine unidentified DNA is presented. See In re Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988) (experimentation to practice invention must not be "undue" for invention to be considered enabled).

The PTO points out that for biochemical processes relating to gene modification, protein expression, and immune response, success is not assured. However, generic inventions are not thereby invalid. Precedent distinguishes among generic inventions that are adequately supported, those that are merely a "wish" or "plan," the words of Fiers v. Revel, 984 F.2d at 1171, and those in between, as illustrated by Noelle v. Lederman, 355 F.3d at 1350; the facts of the specific case must be evaluated. The Board did not discuss the generic concept that both Capon and Eshhar described -- the concept of selecting and combining a gene sequence encoding the variable domain of an antibody and a sequence encoding a lymphocyte activation protein, into a single DNA sequence which, upon expression, allows for immune responses that do not occur in nature. The record does not show this concept to be in the prior art, and includes experimental verification as well as potential variability in the concept.

Whether the inventors demonstrated sufficient generality to support the scope of some or all of their claims, must be determined claim by claim. The Board did not discuss the evidence with respect to the generality of the invention and the significance of the specific examples, instead simply rejecting all the claims for lack of a complete chimeric DNA sequence. As we have discussed, that reasoning is inapt for this case. The Board's position that the patents at issue were merely an "invitation to experiment" did not distinguish among the parties' broad and narrow claims, and further concerns enablement more than written description. See Adang v. Fischhoff, 286 F.3d 1346, 1355 (Fed. Cir.

2002) (enablement involves assessment of whether one of skill in the art could make and use the invention without undue experimentation); In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993) (same). Although the legal criteria of enablement and written description are related and are often met by the same disclosure, they serve discrete legal requirements.

The predictability or unpredictability of the science is relevant to deciding how much experimental support is required to adequately describe the scope of an invention. Our predecessor court summarized in In re Storrs, 245 F.2d 474, 478 (CCPA 1957) that "[i]t must be borne in mind that, while it is necessary that an applicant for a patent give to the public a complete and adequate disclosure in return for the patent grant, the certainty required of the disclosure is not greater than that which is reasonable, having due regard to the subject matter involved." This aspect may warrant exploration on remand.

In summary, the Board erred in ruling that §112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field. However, the Board did not explore the support for each of the claims of both parties, in view of the specific examples and general teachings in the specifications and the known science, with application of precedent guiding review of the scope of claims.

We remand for appropriate further proceedings.

VACATED AND REMANDED

LeCointe, Michelle

From: Julien SAYETTAT @ BREESE DERAMBURE MAJEROWICZ [js@bredema.com]
Sent: Tuesday, September 06, 2005 5:10 AM
To: LeCointe, Michelle
Subject: Y/REF: 069208.0111 - O/REF: 10M486-03012US - US Patent application N° 10/364,540

Michelle,

I revert to you concerning the final action issued on the above mentioned patent application.

In response to this action, my understanding is that we have to amend claim 1 in order to better define "of the same type" and "calendared"

Concerning "of the same type", the specification clarifies the meaning as: layers of material having substantially the same composition, porosity and physico-chemical properties, that is to say substantially the same leucocyte-retention capacity (page 6, first full paragraph).

Concerning "calendared", the specification indicates: the calendaring makes it possible in particular to reduce the mean porosity and air permeability of the layer, which increases its leucocyte-retention capacity (page 6, last paragraph).

Do you think it is relevant to amend claim 1 with those precisions, in particular with:

... said medium comprising a plurality of stacked layers having an upstream side and a downstream side, said layers are formed from at least one porous non-woven material and having substantially the same composition, porosity and physico-chemical properties, that is substantially the same leucocyte-retention capacity, wherein the mean porosity and air permeability of at least one layer are reduce by pressing it by calendaring prior to the stacking thereof in order to increase its leucocyte-retention capacity, said at least one ...

Concerning the argumentation, I think we can use substantially the same as in response of the first action, that is:

- EP'993 fails to teach that a calendared layer would increase the leucocyte-retention capacity;
- EP'993 concerns a membrane, not a porous non-woven material layer;
- Prior art fails to teach the use of layers having the same composition, with at least one downstream layer having smaller porosity and permeability than the others layers.

I thank you to prepare a draft of response and to submit it to me before filing.

Should you need further information, please feel free to contact me.

Yours truly,

Julien SAYETTAT

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